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ORIGINAL STUDY

Predicting the age at natural menopause in middle-aged women

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Abstract

Objective: To predict the age at natural menopause (ANM).

Methods: Cox models with time-dependent covariates were utilized for ANM prediction using longitudinal data from 47 to 55-year-old women ($n = 279$) participating in the Estrogenic Regulation of Muscle Apoptosis study. The ANM was assessed retrospectively for 105 women using bleeding diaries. The predictors were chosen from the set of 32 covariates by using the lasso regression (model 1). Another easy-to-access model (model 2) was created by using a subset of 16 self-reported covariates. The predictive performance was quantified with *c*-indices and by studying the means and standard deviations of absolute errors (MAE $\pm$ SD) between the predicted and observed ANM.

Results: Both models included alcohol consumption, vasomotor symptoms, self-reported physical activity, and relationship status as predictors. Model 1 also included estradiol and follicle-stimulating hormone levels as well as SD of menstrual cycle length, while model 2 included smoking, education, and the use of hormonal contraception as additional predictors. The mean c-indices of 0.76 (95% CI 0.71-0.81) for model 1 and 0.70 (95% CI 0.65-0.75) for model 2 indicated good concordance between the predicted and observed values. MAEs of 0.56 ± 0.49 and 0.62 ± 0.54 years respectively for model 1 and 2 were clearly smaller than the MAE for predicted sample mean (1.58 ± 1.02).

Conclusions: In addition to sex hormone levels, irregularity of menstrual cycle, and menopausal symptoms, also life habits and socioeconomic factors may provide useful information for ANM prediction. The suggested approach could add value for clinicians' decision making related to the use of contraception and treatments for menopausal symptoms in perimenopausal women.

Key Words: Final menstrual period – Menopausal transition – Menopause prediction – Perimenopause – Premenopause.

Video Summary: http://links.lww.com/MENO/A743.

Factors related to age at natural menopause (ANM) have been one of the most frequently studied topics in menopause-related research in recent decades due to the many potential clinical implications of ANM. For instance, accurate prediction of ANM would be beneficial for women who are making decisions related to family planning and treatments for menopausal symptoms. Moreover, accurate prediction of ANM would help to identify women likely to have early menopause, which may put them at increased risk for cardiovascular disease, cardiovascular mortality,[1,2] depression[3] as well as osteoporosis[4] and fractures.[5] On the other hand, later ANM has been associated with

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increased risk of breast cancer[6,7] as well as endometrial[8] and ovarian[9] cancer. However, due to the considerable interindividual variation in the ANM as well as the irregularity and long duration of the menopausal transition, predicting the ANM accurately is challenging.[10]

Previous research in predicting the ANM has mostly focused on investigating the predictive performance of only a few predetermined blood-based biomarkers, such as estradiol, follicle-stimulating hormone, and anti-Müllerian hormone levels, or utilized data and methods with time-invariant or categorized continuous covariates.[11-14] Therefore, the objectives of the study was to use longitudinal study design with repeated covariate measurements to 1) investigate the factors associated with the ANM and 2) develop prospective models for predicting the ANM. A comprehensive set of potential predictors were considered and the predictors for the final models were chosen with an automated selection method. In addition to laboratory-assessed characteristics, the predictive performance of easily accessible self-defined covariates that could be useful for clinicians estimating the time to approaching menopause was evaluated.

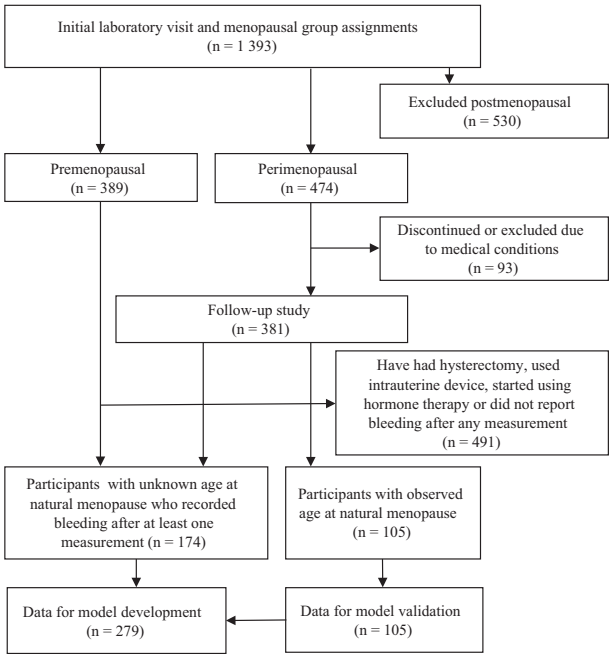

FIG. 1. Flow chart for the study participant selection.

METHODS

Study design

The study was part of the Estrogenic Regulation of Muscle Apoptosis study that has been described in detail elsewhere.[15] In brief, participants were randomly selected from the Digital and Population Data Services Agency (dvv.fi) and a postal invitation were sent to 6,878 women aged 47 to 55 years living in the city of Jyväskylä or neighboring municipalities. Of 2,390 women who responded, decided to continue, and consented, 997 were excluded based on the exclusion criteria. These criteria included several factors and medical conditions that could affect the timing of the final menstrual period or hinder the menopausal group definitions, such as the use of estrogen containing medications, bilateral oophorectomy, pregnancy, lactating, polycystic ovary syndrome, and severe obesity (body mass index $\geq$ 35).

The sample of 1,393 White women were categorized as pre-, peri-, or postmenopausal based on serum follicle-stimulating hormone (FSH) concentrations and self-reported menstrual diaries.[16] The categorization follows the Stages of Reproductive Aging Workshop +10 guidelines[16] although due to technical research reasons a minimum of 6 months follow-up period was used instead of 12 months to verify the postmenopausal status.[15] The participants assigned to the perimenopausal group were invited to a follow-up phase that included keeping menstrual diaries as well as laboratory visits every 3 to 6 months until the participant was categorized as postmenopausal. To avoid misclassification, the FSH concentration was verified with a second measurement about a month after the participant first met the postmenopausal criteria. The participants who have had a hysterectomy, used hormonal intrauterine device, or started using hormone therapy during the follow-up period were excluded from the current study (Fig. 1). The measurements were initiated in the beginning of 2015 and the follow-up period lasted until the end of 2018. All participants provided written informed consent and the study was approved by the ethical committee of the Central Finland Health Care District (No. 8U/2014).

Outcome

All participants in the Estrogenic Regulation of Muscle Apoptosis study were instructed to keep a menstrual diary throughout the study starting at least 12 weeks prior to the baseline measurement. In menstrual diaries, participants reported their daily menstrual bleeding status as bleeding, spotting, or no menstrual bleeding. Bleeding period was defined as at least 1 day of bleeding or 3 or more consecutive days of spotting and spotting days preceding or following bleeding days were considered bleeding days. A single bleeding-free day surrounded by bleeding days was treated as a bleeding day and the surrounding bleeding days were merged into one continuous bleeding period.[17]

For the participants who were perimenopausal in the baseline measurement, went through the follow-up period and had monthly complete bleeding diary, ANM was determined by the age when the last reported bleeding period had started (n = 105). Only the measurements carried out prior to the ANM could be utilized in the analysis and, therefore, all measurements carried out before the menopause were excluded. Finally, there were 296 valid measurements from the participants with known ANM that were used for model development as well as model validation. Additionally, for other participants who were pre- or perimenopausal in the baseline measurement, the last known menstrual period was determined. To make sure that no postmenopausal measurements were included in the analysis,

measurements that were carried out after the last reported bleeding period were excluded. Thus, 391 measurements from 174 participants with unknown time to menopause were also used for model development as censored observations.

Consequently, in addition to data from participants with known ANM, also the data from participants with unknown ANM were used for the development of the models. This data set included 687 separate measurements from 279 participants. However, for the validation of the models, only the data from 105 participants with known ANM could be utilized.

Covariates

The data set consisted of 32 covariates describing characteristics that have been associated with ANM or have been reported to fluctuate during menopausal transition.[18-20] They included several blood-based biomarkers, body composition variables, objectively measured physical activity, menstrual cycle characteristics as well as self-reported variables related to gynecologic history, menopausal symptoms, life habits, and socioeconomic status. They were assessed during every laboratory visit in baseline and follow-up measurements with self-report questionnaires and various measurements. The baseline visits were scheduled to occur at the beginning of the menstrual cycle for participants with regular or predictable menstrual cycles. Most of the candidate predictors were time varying and their values were updated after each laboratory visit. However, self-report variables such as age at menarche, parity, number of pregnancies, and education level (secondary, tertiary) were considered time-invariant and their baseline measurement value was used throughout the study. The questionnaire and measurements that were used are described in more detail elsewhere.[15]

During the laboratory visits, blood samples were taken, and anthropometrics were measured after overnight fasting. IMMULITE 2000 XPi (Siemens Healthineers AG, Erlangen, Germany) was used to measure FSH and estradiol (E2) levels from which the FSH/E2 -ratio was also computed. Furthermore, fasting blood glucose, triglyceride, total cholesterol as well as high- and low-density lipoprotein cholesterol levels were measured. Fat free mass, fat mass, and body fat percentage were assessed using InBody 720 multifrequency bioelectrical impedance analyzer (Biospace Co. Ltd, Seoul, Korea). Body mass and height were measured with standard procedures and body mass index (BMI) was computed by dividing the body mass with the square of the body height.

Menstrual cycle characteristics were determined by using the menstrual diaries and included covariates were menstrual cycle length mean and standard deviation as well as range of menstrual cycle length that was determined as the difference between the longest and shortest recorded menstrual cycle. The length of one cycle was determined in days from the start of bleeding period to the end of the following bleeding-free period and at least two fully recorded cycles was required for a valid covariate value.

Menopausal symptoms were recorded using structured questionnaires in which the participants were asked to report what kind of menopausal symptoms they had experienced. The reported symptoms were merged into four categories that were vasomotor symptoms (eg, sweating and hot flashes), somatic or pain (eg, headache and joint pain), psychological symptoms (eg, sleeping problems and mood swings) and urogenital problems (eg, vaginal symptoms and urinary tract problems).[21] Furthermore, the self-report questionnaires were used to determine the use of hormonal contraception (never, former), relationship status (single, in relationship), smoking status (never, former, current), alcohol consumption in portions per week and physical workload (light, moderate, heavy, very heavy) that describes the occupational physical activity.

Physical activity level was assessed using ActiGraph GT3X and wGT3X accelerometers (ActiGraph LLC, Pensacola, FL). The data were collected at 60 Hz, filtered, and converted into 60-second epochs. The daily mean of total counts and time spent in moderate-to-vigorous activities with tri-axial vector magnitude cut-off point of 6,166 counts per minute normalized to 16-hour wearing time was used.[22,23] Valid measurements included three or more days with more than 10 hours of wear time. Additionally, since self-report physical activity measures capture different aspects of physical behavior compared with accelerometers, two self-report measures focusing on the leisure-time physical activity were included in the analysis. They were a single seven-level scale question [23] and a four-item questionnaire with questions related to commuting as well as average intensity, duration, and frequency of leisure time physical activity that were used for assessing physical activity in MET-hours per day.[24]

Missing data

Of 279 participants in the study, the ANM was determined from 105. The other 174 participants were treated as censored observations in the analysis. The percentage of missing values across the 32 covariates varied between 0% and 28% (Table 1). In total 1,602 covariate records out of 23,358 (7%) were incomplete. Missing data occurred due to incomplete or unclear questionnaire responses and bleeding diaries as well as invalid or missing measurements. Missing data were assumed to occur at random and multiple imputation was used to create and analyze 50 multiply imputed data sets. Multiple imputation was carried out in R (R Foundation for Statistical Computing, Vienna, Austria) using the ''mice'' package.[25] The parameters of substantive interest were estimated in each imputed dataset separately and combined using Rubin's rules.[26]

Multiple imputation was carried out recursively one measurement at a time starting from the baseline measurement. That is, the imputed values of the previous measurement were utilized for the imputation of current measurement. The predictors for the imputation of each variable measured at the same time point were chosen based on their associations with the target variable and missing data values.[27] Additionally, the value of target variables in the previous and following time points were used as the predictors in imputation if they existed. The number of iterations in the imputation algorithm

TABLE 1. *Characteristics of study population, the distribution of all candidate predictors, and the number of missing data values*

	Participants with known ANM ($n = 105$)	All participants ($n = 279$)	All measurements ($n = 687$)	Missing data value[a] n (%)
Blood-based biomarkers				
Total cholesterol [mmol/L]	5.33 ± 0.92	5.31 ± 0.89	5.31 ± 0.90	19 (2.8)
Low-density lipoprotein cholesterol [mmol/L]	2.96 ± 0.77	3.05 ± 0.80	3.03 ± 0.80	19 (2.8)
High-density lipoprotein cholesterol [mmol/L]	1.83 ± 0.42	1.73 ± 0.44	1.75 ± 0.43	19 (2.8)
Blood glucose [mmol/L]	5.24 ± 0.59	5.21 ± 0.60	5.25 ± 0.57	19 (2.8)
Triglycerides [mmol/L]	1.06 ± 0.44	1.09 ± 0.54	1.06 ± 0.53	20 (2.9)
Estradiol [nmol/L]	0.44 ± 0.37	0.42 ± 0.40	0.43 ± 0.45	0 (0.0)
Follicle-stimulating hormone [IU/L]	44.4 ± 30.0	31.6 ± 29.7	32.0 ± 27.6	0 (0.0)
FSH/E2 [IU/pmol]	0.41 ± 1.41	0.28 ± 1.00	0.23 ± 0.69	0 (0.0)
Anthropometrics and body composition				
Body mass index [kg/m^2][b]	25.7 ± 4.1	25.9 ± 3.8	25.9 ± 3.8	17 (2.5)
Fat free mass [kg]	46.6 ± 5.3	47.3 ± 5.3	47.4 ± 5.2	17 (2.5)
Fat mass [kg]	23.1 ± 9.0	22.7 ± 8.2	22.7 ± 8.3	17 (2.5)
Body fat percentage	32.3 ± 7.9	31.6 ± 7.7	31.5 ± 7.6	17 (2.5)
Menstrual cycle characteristics				
Cycle length mean [d]	49.8 ± 21.9	39.9 ± 19.3	38.0 ± 17.1	189 (27.5)
Cycle length standard deviation [d]	30.1 ± 22.5	20.6 ± 21.7	18.7 ± 17.8	189 (27.5)
Cycle length range [d]	71.7 ± 50.5	57.1 ± 56.4	52.6 ± 46.8	189 (27.5)
Menopausal symptoms and gynecological history				
Vasomotor symptoms[b,c]				8 (1.2)
No	11 (10.5)	93 (34.3)	214 (31.5)	
Yes	94 (89.5)	178 (65.7)	465 (68.5)	
Somatic or pain symptoms[b,c]				8 (1.2)
No	59 (56.2)	197 (72.7)	446 (65.7)	
Yes	46 (43.8)	74 (27.3)	233 (34.3)	
Psychological symptoms[b,c]				8 (1.2)
No	33 (31.4)	123 (45.4)	294 (43.3)	
Yes	72 (68.6)	148 (54.6)	385 (56.7)	
Urogenital symptoms[b,c]				8 (1.2)
No	59 (56.2)	174 (64.2)	433 (63.8)	
Yes	46 (43.8)	97 (35.8)	246 (36.2)	
Use of hormonal contraception[b,c]				10 (1.5)
Never	89 (84.8)	216 (80.0)	536 (79.2)	
Former	16 (15.2)	54 (20.0)	141 (20.8)	
Age at menarche [yr.][b,d]	13 (1.3)	13 (2)	13 (2)	18 (2.6)
Parity[b,d]	2 (2)	2 (2)	2 (2)	12 (1.7)
Pregnancies[b,d]	2 (2)	2 (2)	2 (3)	14 (2.0)
Physical activity				
Accelerometer, MVPA [min/d]	50.6 ± 31.8	48.7 ± 27.3	51.5 ± 29.6	114 (16.6)
Accelerometer, Counts $\times 10^5$	6.11 ± 2.01	6.19 ± 1.78	6.34 ± 1.90	114 (16.6)
PA questionnaire [MET×h/d][b]	4.43 ± 4.13	4.32 ± 4.18	4.41 ± 4.37	18 (2.6)
Single seven-level scale question[b,c]				17 (2.5)
1	1 (1.0)	10 (3.7)	30 (4.5)	
2	5 (4.9)	22 (8.2)	49 (7.3)	
3	10 (9.7)	24 (9.0)	53 (7.9)	
4	31 (30.1)	63 (23.5)	168 (25.1)	
5	43 (41.7)	102 (38.1)	244 (36.4)	
6	12 (11.7)	44 (16.4)	120 (17.9)	
7	1 (1.0)	3 (1.1)	6 (0.9)	
Life habits and other self-report variables				
Alcohol consumption [portions/wk][b]	4.30 ± 4.21	3.62 ± 3.72	3.60 ± 3.73	17 (2.5)
Smoking[b,c]				21 (3.1)
Never	75 (72.8)	180 (67.2)	457 (68.6)	
Former	26 (25.2)	72 (26.9)	169 (25.4)	
Current	2 (1.9)	16 (5.9)	40 (6.0)	
Education[b,c]				10 (1.5)
Secondary	52 (49.5)	140 (51.9)	366 (54.1)	
Tertiary	53 (50.5)	130 (48.1)	311 (45.9)	
Relationship status[b,c]				18 (2.6)
Single	18 (17.5)	61 (22.8)	163 (24.4)	
In relationship	85 (82.5)	207 (77.2)	506 (75.6)	
Physical workload[b,c]				78 (11.4)
Light	48 (51.1)	135 (55.1)	316 (51.9)	
Moderate	23 (24.5)	53 (21.6)	139 (22.8)	
Heavy	20 (21.3)	52 (21.2)	148 (24.3)	
Very heavy	3 (3.2)	5 (2.1)	6 (1.0)	

The first two data columns include only the values from the last valid measurement from each participant. Data are mean ± SD unless otherwise specified.

ANM, age at natural menopause; FSH/E2, follicle-stimulating hormone/estradiol; MVPA, moderate-to-vigorous physical activity; PA, physical activity.

[a]Missing data rates illustrated in data set that includes all measurements.

[b]Easily accessible predictor.

[c]Data are n (%).

[d]Data are median (IQR).

was set to 50 and passive imputation was used for derived variables, such as FSH/E2 -ratio and body fat percentage.

Model selection and validation

Cox regression models with time-varying covariates[28] and age as time scale[29] were used for predicting the ANM. The proportional hazards assumption of the Cox models was tested using Schoenfeld residuals and the model selection was carried out using the lasso (Least Absolute Shrinkage and Selection Operator) regression[30] in two separate sets of candidate predictors. The first set included all 32 candidate predictors and the second set included only 16 of them that could be measured without any clinical measurement devices and long-term diaries. Thus, the second set included all self-report covariates as well as BMI (Table 1) and the aim of using this set of candidate predictors was to investigate the predictive performance of easily accessible covariates that a woman can effortlessly provide herself without expert assistance.

The model selection was done in R using the ''penalized'' package.[31] The optimal value of the tuning parameter lambda was initially chosen separately for all 50 imputed data sets using cross-validation and the covariates of interest were selected as the intersection of all predictor sets. However, the optimal lambda value resulted in 19 covariates of interest with all candidate predictors and in 11 covariates of interest with easily accessible candidate predictors which might lead to overfitting with current data set with effective sample size of 105. Thus, based on the good average requirement presented by Harrell[32] in which the maximum number of predictors should be less than effective sample size divided by 15, we increased the lambda value to limit the number of covariates of interest to seven.

The predictive performance of fitted models was quantified using pooled concordance index c[32] and leave-one-out cross-validation that was used for studying the errors between the predicted and observed ANM. The mean of the median survival times from all 50 complete data sets was used for prediction. Bootstrap validation with 200 resamples in 1 randomly selected imputed data set was used to estimate how accurately the models predict the ANM on future subjects or subjects not used to develop the model. Additionally, the leave-one-out cross-validation was also used for sensitivity analysis by utilizing only the first measurement from each participant to investigate the predictive performance of the constructed models with longer time from measurement to ANM. Analysis was carried out in R using the ''rms'' package.[33]

RESULTS

Characteristics of study population

With the notation of mean ± standard deviation, the age of the participants in the baseline measurement was 51.2 ± 1.8 with minimum of 48.6 and maximum of 57.4 years. The number of valid measurement time points varied from 1 to 9 for each participant. In the complete data set of 279 participants, the number of participants with specific number of measurement time points in order from 1 to 9 was 143, 37, 24, 23, 26, 13, 8, 3, and 2. Respective numbers for participants with known ANM ($n = 105$) were 27, 31, 16, 12, 11, 3, 3, 1, and 1. The mean time between repeated measurements was 163 ± 44 days and the time from the last measurement to ANM varied from 4 to 196 days with the mean of 70 ± 49. Valid full follow-up time varied from 0.00 to 3.67 years with the mean of 0.86 ± 0.97 years. The mean ANM in the study population was 52.8 ± 1.9 years. Other characteristics of the candidate predictors and the number of missing values is given in Table 1.

Constructed models

Among all 50 imputed data sets, the median c-index for models in which the predictors were selected from the set of all available covariates (model 1) was 0.762 with the minimum of 0.755 and maximum of 0.783. Respectively, the median c-index for the model in which the predictors were selected from the set of easily accessible covariates (model 2) was 0.701 with the minimum of 0.694 and maximum of 0.706. The model predictors as well as pooled model hazard ratios, P values, and c-indices are given in Table 2.

Model validation

The predictive performance of the models was measured by the mean absolute error (MAE) between the predicted and observed values (Table 3). The MAEs for model 1 (0.56 y) and model 2 (0.62 y) were clearly smaller than the MAE (1.58 y) for the model that used the sample mean as the prediction. The distributions of model errors are illustrated in Figure 2. Furthermore, leave-one-out cross-validation indicated that both models 1 and 2 were slightly biased toward predicting younger ANM compared with the observed values. However, mean bias errors were approximately only 1 month (0.09 y) for model 1 and 2 months (0.18 y) for model 2. The bootstrap validation with one randomly selected data set and 200 resamples demonstrates that there was no significant overfitting present with either one of the conducted models with bootstrap estimate of c-index being 0.74 and 0.65 for models 1 and 2, respectively (Table 4).

The sensitivity analysis indicated that the time from measurement to ANM varied from 0.01 to 2.94 years with mean of 0.90 ± 0.72 and the MAEs were 0.55 ± 0.44 years for model 1 and 0.61 ± 0.54 years for model 2 (Supplemental Digital Content 1, http://links.lww.com/MENO/A742). For both models, the MAEs were distinctly smaller for the participants with the time from measurement to ANM varying from 0 to 0.5 years (0.52 ± 0.38 and 0.44 ± 0.32 y, respectively) or 0.5 to 1.5 years (0.36 ± 0.26 and 0.39 ± 0.29 y, respectively) compared to participants with intervals longer than 1.5 years (1.00 ± 0.57 and 1.41 ± 0.56 y, respectively).

DISCUSSION

Our longitudinal study of 279 pre- and perimenopausal women from whom 105 had observed ANM demonstrated that especially higher estradiol and FSH levels, irregular menstrual bleeding, vasomotor symptoms, and higher level

TABLE 2. *Pooled model characteristics*

	Hazard ratio (95% CI)	*P* value	*c*-index (95% CI)[a]
Model 1: Predictors selected from set of all available predictors			
Estradiol [nmol/L]	2.13 (1.42-3.18)	<0.001	0.76 (0.71-0.81)
Follicle-stimulating hormone [IU/L]	1.01 (1.01-1.02)	<0.001	
Cycle length standard deviation [d]	1.02 (1.01-1.03)	<0.001	
Alcohol consumption [portions/wk]	1.07 (1.02-1.12)	0.009	
SR-PA7 (linear)	2.29 (0.55-9.57)	0.257	
Vasomotor symptoms		0.003	
No	1 reference		
Yes	2.68 (1.41-5.12)		
Relationship status		0.182	
Single	1 reference		
In relationship	1.42 (0.85-2.38)		
Model 2: Predictors selected from the set of easily accessible predictors			
Alcohol consumption [portions/wk]	1.06 (1.01-1.12)	0.016	0.70 (0.65-0.75)
SR-PA7 (linear)	1.85 (0.46-7.49)	0.388	
Vasomotor symptoms		<0.001	
No	1 reference		
Yes	3.33 (1.80-6.19)		
Use of hormonal contraception		0.184	
Never	1 reference		
Former	0.68 (0.38-1.21)		
Relationship status		0.245	
Single	1 reference		
In relationship	1.35 (0.81-2.25)		
Smoking			
Never	1 reference		
Former	0.99 (0.61-1.60)	0.959	
Current	0.37 (0.09-1.52)	0.169	
Education		0.297	
Secondary	1 reference		
Tertiary	1.25 (0.82-1.91)		

CI, confidence interval; SR-PA7, single seven-level scale question for physical activity assessment.
[a]Pooled using Rubin's rules for logit transformed index values.

of alcohol consumption are indicators of approaching natural menopause. The two models constructed in the study demonstrated adequate performance for predicting the ANM by reaching the threshold of good ($c \geq 0.7$) but not strong ($c < 0.8$) concordance with the observed values. Furthermore, the predictions of both models were distinctly more accurate compared with using sample mean ANM as the prediction for all participants.

Mostly, the associations observed in the study are in agreement with the literature. However, a novel observation in the study was that the participants tended to increase their self-reported alcohol consumption when approaching the ANM, although previous studies have reported no association[34] or positive association between alcohol consumption and ANM.[35,36] On the other hand, menopausal transition has been previously shown to be a period of instability regarding alcohol consumption[37] and increasing alcohol consumption could potentially be influenced by negative affect, such as depressive symptoms, caused by hormonal changes during the menopausal transition.[38] Furthermore, the observed association between higher estradiol levels and shorter time to natural menopause was interesting considering that estradiol levels are known to decrease during the menopausal transition. Nonetheless, similar associations have been reported previously[34] and they may result from estradiol levels remaining relatively constant until the late perimenopause and even slightly increasing before they start to decrease toward postmenopause.[39]

Covariates, such as educational level, relationship status, physical activity, BMI, parity, and age at menarche, have been frequently associated with ANM,[36,40,41] yet contradictory results have also been reported.[19,34,42] In this study, educational level, relationship status, and physical activity were only weakly associated with ANM; however, they still increased the accuracy of the models if included as predictors. On the other hand, BMI, parity, and age at menarche were not chosen by the lasso regression as predictors in either one of the models. These results that are partially contradictory to

TABLE 3. *Differences between the predicted and observed age at natural menopause computed using leave-one-out cross-validation (n = 104[a])*

	Model 1	Model 2	Predicted sample mean
Observed ANM	52.77 ± 1.89	52.77 ± 1.89	52.77 ± 1.89
Predicted ANM	52.68 ± 1.79	52.59 ± 1.72	52.77 ± 0.00
Bias error[b]	−0.09 ± 0.74	−0.18 ± 0.80	0.00 ± 1.89
Absolute error[b]	0.56 ± 0.49	0.62 ± 0.54	1.58 ± 1.02
Squared error[b]	0.55 ± 0.97	0.67 ± 1.12	3.55 ± 4.01
Pairwise *t* test[b]	*t* = −1.298	*t* = −2.245	
	df = 103	df = 103	
	p = 0.197	p = 0.027	

Data are mean ± SD in years unless otherwise specified.
ANM, age at natural menopause.
[a]Number of participants with valid ANM prediction.
[b]Between observed and predicted values. Pairwise *t* test was not carried out for predicted sample mean since the results would not be meaningful.

FIG. 2. Histograms illustrating the distributions of model errors.

previous findings may result from the unique study design that utilizes information from several measurements carried out during the perimenopause. Thus, unlike most of the previous studies, this study also captures the changes that occur during the menopausal transition in addition to associations of certain covariates with ANM. Furthermore, the predictors for the models were not chosen based on their statistical significance but by optimizing the constructed models.

The greatest strength of the study is the methodological approach including dealing with the missing data values, using models that encompass time-varying covariates, and utilizing an extensive set of candidate predictors with automated model selection. As the participants were a homogenous sample of Finnish middle-aged women, the generalizability of the results is good for populations consisting of Scandinavian White women but poorer for more heterogeneous populations. Furthermore, although assessing the postmenopausal status using bleeding diaries and FSH measurements is considered advantageous compared with retrospective self-reports, the use of a 6-month follow-up period instead of 12 months to verify to postmenopausal status may have led to misclassification for some participants. The age range of 47 to 55 years as well as the exclusion of postmenopausal women in the baseline may have also caused selection bias since women with younger ANM were more likely to be excluded. Other limitations of the study are the data set with relatively small sample size and follow-up time less than 4 years for all participants. This increases the uncertainty in the results and keeps the constructed models from being suited for predicting the ANM for women in their 30s or early 40s. Additionally, some potentially strong predictors of ANM, such as anti-Müllerian hormone levels, follicle counts, or mother's ANM,[43] were not included in the set of candidate predictors because they were not available.

Although the models were constructed with a data set in which the time from last measurement to ANM were less than 7 months for all participants, the sensitivity analysis using only one measurement from each participant demonstrated that the models provide adequate prediction accuracy when using measurements that are carried out up to 18 months before the ANM (Supplemental Digital Content 1, http://links.lww.com/MENO/A742). These are encouraging results indicating that by utilizing a training data set with longer follow-up time and possibly a few additional candidate predictors, the suggested predictors and methodological approach could also be used for discovering the diagnostic rules for predicting ANM for younger premenopausal women.

CONCLUSIONS

Higher estradiol and FSH levels, irregular menstrual cycles, and menopausal symptoms are strong indicators of approaching menopause in middle-aged women. Additionally, information related to life habits and socioeconomic factors, such as alcohol consumption, smoking habits, relationship status, physical activity, and the use of hormonal contraception may provide useful information for assessing the time to natural menopause. The suggested approach for predicting ANM

TABLE 4. *Bootstrap validation of constructed models*

	Original sample	Training sample	Test sample	Optimism	Corrected index	*n*
Model 1						
c-index	0.763	0.775	0.747	0.028	0.735	200
R^2	0.162	0.190	0.135	0.056	0.106	200
Slope[a]	1.000	1.000	0.766	0.233	0.766	200
Model 2						
c-index	0.697	0.715	0.672	0.043	0.654	200
R^2	0.097	0.121	0.070	0.051	0.046	200
Slope[a]	1.000	1.000	0.696	0.304	0.696	200

[a]Calibration slope (slope of predicted log odds vs true log odds).

could be useful for clinicians when making decisions related to the use of hormonal contraception and treatment for menopausal symptoms in perimenopausal women. However, further studies with a similar methodological approach, long-term follow-up time and a more comprehensive set of covariates are warranted to develop models with improved predictive performance that would be applicable in more heterogeneous populations and for women in their 30s or early 40s.

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